

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
11 April 2002 (11.04.2002)

PCT

(10) International Publication Number  
WO 02/28999 A2

- |  |   |   |
|--|---|---|
| (51) International Patent Classification <sup>7</sup> :  | C12N  | (81) Designated States ( <i>national</i> ): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW. |
| (21) International Application Number:   | PCT/US01/30821  | (84) Designated States ( <i>regional</i> ): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BH, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).  |
| (22) International Filing Date:  | 3 October 2001 (03.10.2001)   |   |
| (25) Filing Language:  | English   |   |
| (26) Publication Language:   | English   |   |
| (30) Priority Data:  | 60/237,189                    3 October 2000 (03.10.2000)                    US                                     |   |
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| (74) Agents:   | CARROLL, Lawrence, J. et al.; Morgan, Lewis & Bockius LLP, 1111 Pennsylvania Avenue, NW, Washington, DC 20004 (US). | <i>with sequence listing part of description published separately in electronic form and available upon request from the International Bureau</i>   |



A2

WO 02/28999

(54) Title: GENE EXPRESSION PROFILES IN GRANULOCYTIC CELLS

(57) Abstract: The present invention identifies the global changes in gene expression associated with activation of granulocytes. The present invention also identifies expression profiles which serve as useful diagnostic markers as well as markers that can be used to monitor disease states, disease progression, drug toxicity, drug efficacy and drug metabolism.

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Table 7. Genes identified by DNA chip analysis.

| Affy ID    | Genbank | Seq ID | Gene Bank Names   | ratio ratio ratio |       |       |       |
|------------|---------|--------|---|-------------------|-------|-------|-------|
|            |         |        |   | E.coli            | KM5   | KM6   | yopH  |
| 38119_at   | X12496  | 1097   | Human mRNA for erythrocyte membrane statoglycoprotein beta (glycophorin C).         | 1.0               | 2.8   | 1.8   | 3.2   |
| 985_s_at   | X12830  | 1098   | Human mRNA for Interleukin-6-receptor.  | 1.3               | -1.6  | 1.2   | 3.3   |
| 39239_at   | X13444  | 1099   | Human mRNA for CD8 beta-chain glycoprotein (CD8 beta.1).                            | 5.0               | 18.2  | 31.0  | 16.3  |
| 41231_f_at | X13546  | 1100   | Human HMG-17 gene for non-histone chromosomal protein HMG-17.                       | -1.0              | 1.4   | -1.7  | -1.1  |
| 37033_s_at | X13710  | 1101   | H.sapiens unspliced mRNA for glutathione peroxidase.                                | 1.0               | 2.1   | 2.1   | 2.9   |
| 33820_g_at | X13794  | 1102   | H.sapiens lactate dehydrogenase B gene exon 1 and 2 (EC 1.1.1.27) (and joined CDS). | -5.3              | 2.7   | 2.2   | 1.1   |
| 37180_at   | X14034  | 1103   | Human mRNA for phospholipase C.   | -1.3              | -1.1  | -1.7  | -1.7  |
| 31870_at   | X14046  | 1104   | Human mRNA for leukocyte antigen CD37.  | 1.2               | -3.1  | -2.8  | -2.3  |
| 38610_s_at | X14487  | 1105   | Human gene for acidic (type I) cytokeratin 10.                                      | 1.0               | 1.0   | -2.7  | -1.6  |
| 40415_at   | X14813  | 1106   | Human liver mRNA for 3'-oxoacyl-CoA thiolase.                                       | -5.3              | -30.8 | -5.7  | -3.1  |
| 33480_at   | X15393  | 1108   | H.sapiens motilin gene exon 2 (and joined CDS).                                     | 2.2               | 2.6   | 2.0   | 2.0   |
| 33676_at   | X15940  | 1109   | Human mRNA for ribosomal protein L31.   | -1.0              | -1.2  | -1.4  | 1.4   |
| 1220_g_at  | X15949  | 1110   | Human mRNA for interferon regulatory factor-2 (IRF-2).                              | -4.5              | 1.1   | -2.5  | -1.4  |
| 1219_at    | X15949  | 1110   | Human mRNA for interferon regulatory factor-2 (IRF-2).                              | -4.5              | -18.4 | -16.7 | -18.4 |
| 35201_at   | X16135  | 1112   | Human mRNA for novel heterogeneous nuclear RNP protein, L protein.                  | 1.9               | 2.0   | 1.1   | -1.1  |
| 1919_at    | X16316  | 1113   | Human mRNA for vav oncogene.  | -1.4              | -1.1  | -6.1  | -1.4  |
| 988_at     | X16354  | 1114   | Human mRNA for transmembrane carnoembryonic antigen BGPa (formerly TM1-CEA).        | 1.2               | -2.0  | 1.4   | -6.1  |
| 37021_at   | X16832  | 1116   | Human mRNA for cathepsin H (EC 3.4.22.16).  | -4.3              | 1.5   | -2.4  | -1.5  |
| 36985_at   | X17025  | 1117   | Human homolog of yeast IPP isomerase.   | 1.0               | -2.5  | -1.6  | -1.7  |
| 35338_at   | X17094  | 1119   | Human fur mRNA for furin.   | -5.4              | -13.2 | -13.2 | -13.2 |
| 31527_at   | X17206  | 1120   | Human mRNA for LLRep3.  | -1.1              | -2.3  | -2.8  | -1.7  |
| 32786_at   | X51345  | 1121   | Human jun-B mRNA for JUN-B protein.   | 3.4               | 1.7   | 1.4   | -1.6  |
| 35251_at   | X51435  | 1122   | Human PRDII-BF1 gene for a DNA-binding protein.                                     | -6.2              | 6.1   | 7.6   | 4.3   |
| 40103_at   | X51521  | 1123   | Human mRNA for ezrin.   | 2.8               | 3.2   | 1.5   | 2.0   |
| 35965_at   | X51757  | 1124   | Human heat-shock protein HSP70B' gene.  | -10.9             | -4.9  | -4.0  | -7.3  |
| 117_at     | X51757  | 1124   | Human heat-shock protein HSP70B' gene.  | -10.9             | -10.9 | -5.4  | -3.1  |
| 38515_at   | X51801  | 1125   | Human OP-1 mRNA for osteogenic protein.   | 1.0               | 4.0   | 1.0   | 7.7   |
| 788_s_at   | X52001  | 1126   | Human endothelin 3 (EDN3) mRNA, complete cds.                                       | 2.0               | 1.0   | 1.0   | 10.8  |

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What is claimed is:

1. A method of detecting granulocyte activation, comprising:
  - (a) detecting the level of expression in a sample of one or more genes from  
5 Tables 2-8;
  - (b) comparing the expression level to an expression level in an un-activated granulocyte, wherein differential expression of the genes in Tables 2-8 is indicative of granulocyte activation.
- 10 2. A method of modulating granulocyte activation, comprising:
  - (a) contacting a granulocyte with an agent, wherein the agent alters the expression of at least one gene in Tables 2-8 thereby modulating granulocyte activation.
- 15 3. A method of screening for an agent capable of modulating granulocyte activation, comprising:
  - (a) preparing a first gene expression profile of a cell population comprising granulocytes, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;
  - (b) exposing the cell population to the agent;
  - 20 (c) preparing second gene expression profile of the agent-exposed cell population; and
  - (d) comparing the first and second gene expression profiles.
- 25 4. A method of detecting an inflammation in a tissue, comprising:
  - (a) detecting the level of expression in a sample of the tissue of one or more genes from Tables 2-8; wherein the level of expression of the genes in Tables 2-8 is indicative of inflammation.
- 30 5. A method of treating an inflammation in a tissue, comprising:
  - (a) contacting a tissue having an inflammation with an agent, wherein the agent alters the expression in the tissue of at least one gene in Tables 2-8 thereby treating the inflammation.

6. A method of screening for an agent capable of modulating an inflammation in a tissue, comprising:
- (a) preparing a first gene expression profile of a sample of the tissue, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;
- (b) exposing the tissue to the agent;
- (c) preparing second gene expression profile of the agent-exposed tissue; and
- (d) comparing the first and second gene expression profiles.
- 10 7. A method of detecting a chronic inflammation in a tissue, comprising:
- (a) detecting the level of expression in a sample of the tissue of one or more genes from Tables 2-8; wherein the level of expression of the genes in Tables 2-8 is indicative of a chronic inflammation.
- 15 8. A method of treating a chronic inflammation in a tissue, comprising:
- (a) contacting a tissue having a chronic inflammation with an agent, wherein the agent alters the expression in the tissue of at least one gene in Tables 2-8 thereby treating the chronic inflammation.
- 20 9. A method of screening for an agent capable of modulating a chronic inflammation in a tissue, comprising:
- (a) preparing a first gene expression profile of a sample of the tissue, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;
- 25 (b) exposing the tissue to the agent;
- (c) preparing a second gene expression profile of the agent-exposed tissue; and
- (d) comparing the first and second gene expression profiles.
- 30 10. A method of detecting an allergic response in a subject, comprising:
- (a) obtaining a sample from the subject, the sample comprising granulocytes;
- (b) preparing a gene expression profile of the sample, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;

(c) comparing the expression level to an expression level in a sample from a normal individual, wherein differential expression of the genes in Tables 2-8 is indicative of an allergic response.

5 11. A method of treating an allergic response in a subject, comprising:

(a) administering to the subject an agent, wherein the agent alters the expression in the tissue of at least one gene in Tables 2-8 thereby treating the allergic response.

10 12. A method of screening for an agent capable of modulating an allergic response in a subject, comprising:

(a) preparing a first gene expression profile of a sample from the subject, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;

15 (b) administering to the subject an agent;

(c) preparing a second gene expression profile of a sample from the agent-exposed subject; and

(d) comparing the first and second gene expression profiles.

20 13. A method of detecting exposure of a subject to a pathogen, comprising:

(a) preparing a first gene expression profile of a granulocyte population from the subject, wherein the expression profile determines the expression level of one or more genes from Tables 2-8;

25 (b) comparing the first gene expression profile to a second gene expression profile from a granulocyte population exposed to the pathogen and to a third gene expression profile from a granulocyte population not exposed to the pathogen; and

(c) determining whether the subject was exposed to the pathogen.

14. A method of treating a subject exposed to a pathogen, comprising:

30 (a) administering to the subject an agent, wherein the agent affects the expression of at least one gene in Tables 2-8 thereby treating the subject.

15. A method of screening for an agent that modulates a response of a granulocyte population to a pathogen, comprising:

(a) preparing a first gene expression profile of a first sample from the granulocyte population, wherein the expression profile determines the expression level of 5 one or more genes from Tables 2-8;

(b) exposing a second sample of the granulocyte population to a pathogen and preparing a second gene expression profile from the second sample;

(c) contacting the pathogen-exposed granulocyte population with an agent and preparing a third gene expression profile from the agent-contacted pathogen-exposed 10 population;

(d) comparing the first, second and third gene expression profiles; and

(e) identifying agents that modulate the response of a granulocyte population to the pathogen.

15 16. A method of detecting a sterile inflammatory disease in a subject, comprising:

(a) detecting the level of expression in a sample from the subject of one or more genes from Tables 2-8; wherein the level of expression of the genes in Tables 2-8 is indicative of a sterile inflammatory disease.

20 17. A method of treating a sterile inflammatory disease in a subject, comprising:

(a) contacting the subject with an agent, wherein the agent alters the expression in the tissue of at least one gene in Tables 2-8 thereby treating the sterile 25 inflammatory disease.

18. A method of screening for an agent capable of modulating a sterile inflammatory disease in a subject, comprising:

(a) preparing a first gene expression profile of a sample from the subject, 30 wherein the expression profile determines the expression level of one or more genes from Tables 2-8;

(b) exposing the subject to the agent;

(c) preparing second gene expression profile of a sample obtained from the

agent-exposed subject; and

(d) comparing the first and second gene expression profiles.

19. A composition comprising at least two oligonucleotides, wherein each of  
5 the oligonucleotides comprises a sequence that specifically hybridizes to a gene in Tables  
2-8.

20. A composition according to claim 19, wherein the composition comprises  
at least 3 oligonucleotides, wherein each of the oligonucleotides comprises a sequence that  
10 specifically hybridizes to a gene in Tables 2-8.

21. A composition according to claim 19, wherein the composition comprises  
at least 5 oligonucleotides, wherein each of the oligonucleotides comprises a sequence that  
specifically hybridizes to a gene in Tables 2-8.  
15

22. A composition according to claim 19, wherein the composition comprises  
at least 7 oligonucleotides, wherein each of the oligonucleotides comprises a sequence that  
specifically hybridizes to a gene in Tables 2-8.

20 23. A composition according to claim 19, wherein the composition comprises  
at least 10 oligonucleotides, wherein each of the oligonucleotides comprises a sequence  
that specifically hybridizes to a gene in Tables 2-8.

24. A composition according to any one of claims 19-23, wherein at least one  
25 oligonucleotide is attached to a solid support.

25. A composition according to claim 24, wherein the solid support is selected  
from a group consisting of a membrane, a glass support, a filter, a tissue culture dish, a  
polymeric material, a bead and a silica support.  
30

26. A solid support comprising at least two oligonucleotides, wherein each of  
the oligonucleotides comprises a sequence that specifically hybridizes to a gene in Tables  
2-8.

27. A solid support according to claim 26, wherein at least one of the oligonucleotides is covalently attached to the solid support.

5 28. A solid support according to claim 26, wherein at least one of the oligonucleotides is non-covalently attached to the solid support.

29. A solid support according to claim 26, wherein the support comprises at least 10 different oligonucleotides in discrete locations per square centimeter.

10 30. A solid support according to claim 26, wherein the support comprises at least 100 different oligonucleotides in discrete locations per square centimeter.

31. A solid support according to claim 26, wherein the support comprises at 15 least 1000 different oligonucleotides in discrete locations per square centimeter.

32. A solid support according to claim 26, wherein the support comprises at least 10,000 different oligonucleotides in discrete locations per square centimeter.

20 33. A computer system comprising:

(a) a database containing information identifying an expression level in a cell population comprising granulocytes of a set of genes comprising at least two genes in Tables 2-8; and

(b) a user interface to view the information.

25 34. A computer system of claim 33, wherein the database further comprises sequence information for the genes.

35. A computer system of claim 33, wherein the database further comprises 30 information identifying the expression level for the set of genes in a cell population comprising non-activated granulocytes.

36. A computer system of claim 33, wherein the database further comprises information identifying the expression level of the set of genes in a cell population comprising activated granulocytes.

5 37. A computer system of any of claims 33-36, further comprising records including descriptive information from an external database, which information correlates said genes to records in the external database.

10 38. A computer system of claim 37, wherein the external database is GenBank.

39. A method of using a computer system of any one of claims 33-36 to present information identifying the expression level in a tissue or cell of at least one gene in Tables 2-8, comprising:

15 (a) comparing the expression level of at least one gene in Tables 2-8 in the tissue or cell to the level of expression of the gene in the database.

40. A method of claim 39, wherein the expression level of at least two genes are compared.

20 41. A method of claim 39, wherein the expression level of at least five genes are compared.

42. A method of claim 39, wherein the expression level of at least ten genes are compared.

25 43. A method of claim 39, further comprising displaying the level of expression of at least one gene in the tissue or cell sample compared to the expression level in a cell population comprising activated granulocytes.

30 44. A method of identifying virulence factor genes in a pathogen, comprising:  
(a) preparing a first gene expression profile of a quiescent granulocyte population;  
(b) preparing a second gene expression profile of a granulocyte population

- exposed to a virulent or avirulent strain of pathogen;
- (c) preparing a third gene expression profile from a granulocyte population exposed to a strain of pathogen with a mutation in a putative virulence factor gene; and
- (d) comparing the first, second and third gene expression profiles to identify  
5 a virulence factor gene of the pathogen.

ID ABK84542 standard; cDNA; 2757 BP.  
XX  
AC ABK84542;  
XX  
DT 14-AUG-2002 (first entry)  
XX  
DE Human cDNA differentially expressed in granulocytic cells #1113.  
XX  
KW Human; ss; granulocytic cell; DNA chip; bacterial infection;  
KW viral infection; parasitic infection; protozoal infection;  
KW fungal infection; sterile inflammatory disease; psoriasis;  
KW rheumatoid arthritis; glomerulonephritis; asthma; thrombosis;  
KW cardiac reperfusion injury; renal reperfusion injury; ARDS;  
KW adult respiratory distress syndrome; inflammatory bowel disease;  
KW Crohn's disease; ulcerative colitis; periodontal disease;  
KW granulocyte activation; chronic inflammation; allergy.  
XX  
OS Homo sapiens.  
XX  
PN WO200228999-A2.  
XX  
PD 11-APR-2002.  
XX  
PF 03-OCT-2001; 2001WO-US30821.  
XX  
PR 03-OCT-2000; 2000US-237189P.  
XX  
PA (GENE-) GENE LOGIC INC.  
XX  
PI Beazer-Barclay Y, Weissman SM, Yamaga S, Vockley J;  
XX  
DR WPI; 2002-435328/46.  
XX  
PT Detecting granulocyte activation by detecting differential expression  
PT of genes associated with granulocyte activation, which serves as  
PT diagnostic markers that is useful for monitoring disease states and  
PT drug toxicity -  
XX  
PS Claim 1; SEQ ID No 1113; 114pp; English.  
XX  
CC The invention relates to detecting (M1) granulocyte (GC) activation  
CC (GCA), by detecting the level of expression of gene(s) (Gs) identified by  
CC DNA chip analysis as given in the specification, and comparing  
CC the expression level to an expression level in an unactivated  
CC GC, where differential expression of Gs is indicative of GCA.  
CC Also included are modulating (M2) GA by contacting GC with an agent  
CC that alters the expression of at least one gene in Gs; (2) screening (M3)  
CC for an agent capable of modulating GCA or an inflammation (especially  
CC chronic) in a tissue, an allergic response in a subject, exposure of a  
CC subject to a pathogen or sterile inflammatory disease using the  
CC gene expression profile; (3) detecting (M4) an inflammation (especially  
CC chronic) in a tissue, an allergic response in a subject, exposure of a  
CC subject to a pathogen or sterile inflammatory disease, by detecting the  
CC level of expression in a sample of the tissue of gene(s) from Gs, where  
CC the level of expression of the gene is indicative of inflammation;  
CC (4) treating (M5) an inflammation (especially chronic) or in a tissue,  
CC an allergic response in a subject, exposure of a subject to a pathogen  
CC or sterile inflammatory disease, by contacting a tissue having  
CC inflammation with an agent that modulates the expression of gene(s)  
CC from Gs in the tissue. M1 is useful for detecting GCA; M2 is useful for  
CC modulating GA; M3 is useful for screening an agent capable of modulating  
CC GCA preferably in an inflammation in a tissue; M4 is useful for  
detecting an inflammation (especially chronic) in a tissue, an allergic  
CC response in a subject, exposure of a subject to a pathogen or sterile

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CC inflammatory disease (e.g. psoriasis, rheumatoid arthritis,  
 CC glomerulonephritis, asthma, thrombosis, cardiac reperfusion injury, renal  
 CC reperfusion injury, ARDS, adult respiratory distress syndrome,  
 CC inflammatory bowel disease, Crohn's disease, ulcerative colitis,  
 CC periodontal disease; also bacterial infection, viral infection,  
 CC parasitic infection, protozoal infection, fungal infection and M5 is  
 CC useful for treating one of the above conditions. The present  
 CC sequence represents a gene differentially expressed in granulocytes.  
 CC Note: The sequence data for this patent did not form part  
 CC of the printed specification, but was obtained in electronic  
 CC format directly from WIPO at  
 CC ftp.wipo.int/pub/published\_pct\_sequences.

XX

SQ Sequence 2757 BP; 693 A; 713 C; 809 G; 542 T; 0 other;

|             |             |             |             |             |              |      |
|-------------|-------------|-------------|-------------|-------------|--------------|------|
| ctaggcttt   | gcaaaaagct  | tcacgctgcc  | gcaagcactc  | agggcgcaag  | ggctgctaaa   | 60   |
| ggaagcgaa   | cacgttagaaa | gccagtcgc   | agaaacggtg  | ctgaccgg    | atgaatgtca   | 120  |
| gctactggc   | tatctggaca  | agggaaaacg  | caagcgaaa   | gagaaagcag  | ttccctgtgcc  | 180  |
| ttaagaacat  | tagaaccttc  | ctgtccacct  | gctgtgagaa  | gttcggcctc  | aagcggagcg   | 240  |
| agcttgcga   | agcctttgac  | ctcttcgatg  | tgcaggatt   | tggcaaggtc  | atctacaccc   | 300  |
| tgtctgcct   | gtctctggacc | ccgatcgccc  | agaacagggg  | gatcatgccc  | ttccccaccg   | 360  |
| aggaggagag  | tgttaggtgat | gaagacatct  | acagtggct   | gtccgaccag  | atcgacgaca   | 420  |
| cggtgagga   | ggatgaggac  | ctgtatgact  | gcgtggagaa  | tgaggaggcg  | gaaggcgacg   | 480  |
| agatctatga  | ggacctcatg  | cgctcggagc  | ccgtgtccat  | gccggccaag  | atgacagagt   | 540  |
| atgacaagcg  | ctgctgctgc  | ctgcgggaga  | tccagcagac  | ggaggagaag  | tacactgaca   | 600  |
| cgctgggctc  | catccagcag  | catttctga   | agcccctgca  | acggttcctg  | aaacctcaag   | 660  |
| acattgagat  | catcttatac  | aacattgagg  | acctgcttcg  | tgttcatact  | cacttcctaa   | 720  |
| aggagatgaa  | ggaagccctg  | ggcacccctg  | gcmcaccgaa  | tctctaccag  | gtcttcatca   | 780  |
| aataacaagga | gagttcctc   | gtctatggcc  | gctactgcag  | ccaggtggag  | tcagccagca   | 840  |
| aacaccttga  | ccgtgtggcc  | gcagcccccgg | aggacgtgca  | gatgaagctg  | gaggaatgtt   | 900  |
| ctcagagagc  | caacaacggg  | agttcactg   | cgcgacctgc  | tgtatgtgcc  | tatgcagcga   | 960  |
| gttctcaaat  | atcacctcct  | tctccaggag  | ctggtaaaac  | acacgcagga  | ggcgatggag   | 1020 |
| caaggaaact  | gcfgctggcc  | ctggatgcca  | tgagggaccc  | ggctcagtgc  | gtgaacgagg   | 1080 |
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| tctgttaagcg | caggggagac  | tccttatgacc | tcaaggactt  | tgtaaacctg  | cacagcttcc   | 1320 |
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| ttggaccctt  | tctacggctc  | aaccctggag  | acattgtgga  | gctcacgaa   | gctgaggctg   | 1860 |
| aacagaactg  | gtgggagggc  | agaaatacat  | ctactaatga  | aattggctgg  | tttccttgta   | 1920 |
| acagggtgaa  | gccatatgtc  | catggccctc  | ctcaggaccc  | gtctgttcat  | ctctggtaac   | 1980 |
| caggccccat  | ggagcgggca  | ggggcagaga  | gcatcctggc  | caaccgctcg  | gacgggactt   | 2040 |
| tcttggtgcg  | gcagaggggt  | aaggatgcag  | cagaatttgc  | catcagcatt  | aaatataacg   | 2100 |
| tcgaggtcaa  | gcacacgggt  | aaaatcatga  | cagcagaagg  | actgtaccgg  | atcacagaga   | 2160 |
| aaaaggcttt  | ccgggggctt  | acggagctgg  | tggagttta   | ccagcagaac  | tctctaaagg   | 2220 |
| attgcttcaa  | gtctctggac  | accaccttgc  | agttcccctt  | caaggagcct  | aaaaagagaa   | 2280 |
| ccatcagcag  | gccagcagt   | ggaagcacaa  | agtattttgg  | cacagccaaa  | gcccgtatg    | 2340 |
| acttctgccc  | ccgtgaccgt  | tcagagctgt  | cgctcaagga  | gggtgacatc  | atcaagatcc   | 2400 |
| ttaacaagaa  | gggacagcaa  | ggctggggc   | gagggggagat | ctatggccgg  | gttggctgg    | 2460 |
| tccctgccaa  | ctacgtggag  | gaagattatt  | ctgaataactg | ctgagccctg  | gtgccttgcc   | 2520 |
| agagagacga  | gaaactccag  | gctctgagcc  | cggcgtggcg  | aggcagcga   | ccagggctg    | 2580 |
| tgacagctcc  | ggcggtgtga  | gactttggga  | tgactggag   | gaggccagcg  | tccagctggc   | 2640 |
| ggtgctccc   | ggatgtgccc  | tgacatggtt  | aatttataac  | accccgattt  | tcctcttggg   | 2700 |
| tcccctcaag  | cagacggggg  | ctcaaggggg  | ttacattaa   | taaaaggatg  | aagatgg      | 2757 |

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